

Remarks

In the Office Action, the Examiner noted that claims 1 to 6 are pending in the application; and that claims 1 to 6 are rejected. By this amendment, claims 1-3, and 5 have been amended. Thus, claims 1 to 6 are pending in the application. No new subject matter has been inserted through these amendments. In particular, the specification was amended at page 10 to provide generic name of DOWEX[®] and to rewrite DOWEX[®] in upper case. Claim 1 was amended to recite the claim more in line with the US format as well as to correct an obvious typographical error in that the spelling of the word "phenoxathienyl" is corrected. Also, the phrase "in the form of base or of salt derived from addition to an acid" is replaced with "or a salt thereof." Support for this can be found at various places in the specification, more specifically at lines 11 to 13 on page 2 and at lines 17 to 21, page 7 where a dihydrobromide salt of Example 1 is made from the free base; line 8, page 8 shows isolation of a hydrobromide salt of Example 2; Example 4 (compound No. 26) beginning at line 19, page 10 describes again a preparation of hydrobromide, etc. Claim 2 has been amended to recite it in the US format. Claims 3 and 5 have been amended to recite specific diseases that can be treated using the compounds of this invention. Support for this can be found in the disclosures beginning at line 20, page 17 to line 18, page 18 of the specification. Thus, it is respectfully submitted that all of the amendments are fully supported by the specification. The Examiner's rejections are traversed below.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 3 and 5 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with written description requirement.

In particular, the Examiner alleges that "The instant methods encompasses as yet unidentified disorders linked to a dysfunction of the nicotinic receptors, as description of which is not found in the specification." Applicants respectfully disagree with this conclusion. It is submitted that claims 3 and 5 are in full compliance with the provisions of written description requirement as stipulated by 35 USC § 112, first paragraph. The Examiner's attention is particularly drawn to specific disclosures beginning at line 2, page 14 of the specification, which concludes at line 18, page 18 of the specification. In these

pages, various biological protocols that can be used to confirm the biological efficacy of the compounds of the invention are provided. Furthermore, various disorders that are affected by the dysfunction of the nicotinic receptors are also provided, thus satisfying the written description requirement of 35 USC 112, first paragraph.

Nevertheless, in order to expedite the prosecution of this case and without acquiescing Applicants' rights, claims 3 and 5 have been amended to provide certain disorders that can be treated by the compounds of this invention. Thus it is submitted that claims 3 and 5, as amended, obviates this rejection. Accordingly, withdrawal of rejection as to claims 3 and 5 under 35 USC 112, first paragraph is respectfully requested.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 1-6 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement.

Specifically, the Examiner alleges that claims 1-6 do not satisfy the enablement requirement using the "eight Wands" factors, and particularly draws attention to: 1) nature of the invention; 2) the state of the prior art and predictability and 3) guidance and working examples. However, contrary to the views of the Examiner, Applicants respectfully submit that each of these Wands factors is fully satisfied by the disclosure and thus by claims 1-6, as amended, and therefore, fully satisfy the provisions of the enablement requirements of 35 USC 112, first paragraph.

More specifically, the nature of the invention is to provide compounds of claims 1 and 2; the pharmaceutical compositions derived therefrom as recited in claims 4 and 6; and the method of treatment of certain disorders due to dysfunction of nicotinic receptors. As to claims 1, 2, 4 and 6, the Examiner's attention is respectfully drawn to specific examples provided in the specification beginning at line 12, page 5. Please note that a total of 72 specific compounds have been made in accordance with various synthetic procedures provided in the specification. Further, all of these compounds were tested for their biological efficacy at the nicotinic receptor, particularly at $\alpha 4\beta 2$ subunit, using the methods described in the art, i.e., the methods of Anderson et al. (Eur. J. Pharmacol. (1994), 253, 261 and Hall et al. (Brain Res. (1993), 600, 127. Complete details of these test methods are provided in the specification beginning at line 2, page 14. Thus it is

submitted that the nature of the invention is fully and unambiguously disclosed in the specification.

As to the state of the prior art and predictability, the Examiner incorrectly analyzes and alleges that “there is no nexus between ‘treat/prevent disorders’ and dysfunction of the nicotinic receptor. Lockheed et al. USP 6407095 and USP 6635645 teach azobicyclo compounds structurally removed compounds, used to treat/prevent disorders associated with a dysfunction of the nicotinic receptor. The skilled artisan would not be motivated to extrapolate the results of structurally removed compounds to the claimed compounds.” Applicants respectfully disagree with this analysis.

Contrary to the views of the Examiner, Applicants respectfully submit that motivation of a skilled artisan is not the proper analysis here. What a skilled artisan is looking in a new series of compounds is whether or not a compound is active at the nicotinic receptor and not a motivation to test a new compound for nicotinic receptor activity. Thus, if in a new disclosure, such as the one in the instant invention, there is sufficient information to show that the compounds as disclosed therein are active at nicotinic receptor, a skilled artisan readily appreciates the intended utility of the compounds without resorting to undue experimentation.

In further support of this assertion, Applicants respectfully draw the attention of the Examiner to the state of the art as it relates to nicotinic receptors. A quick key word search on the Medline database using the phrase “nicotinic receptor” resulted in **8948 hits**, showing that this is a widely studied field. However, a narrowing of this search to look for the phrase “alpha4beta2 nicotinic receptors” still resulted in **450 hits**. This clearly shows that a skilled artisan is well versed with the effects of nicotinic receptors and more particularly $\alpha 4\beta 2$ nicotinic receptor subunits.

In further support of this assertion, Applicants respectfully draw the attention of the Examiner to a recent article by Zwart et al. (Eur. J. Pharmacology, April 5, 2006 (Epub ahead of print), which discloses various aspects of $\alpha 4\beta 2$ nicotinic receptors. A copy of which is enclosed for Examiner’s convenience. More importantly, as stated therein, $\alpha 4\beta 2$ nicotinic receptors are targets for drugs in order to treat a variety of diseases. As specifically stated therein:

"The predominant subtype of nicotinic acetylcholine receptor in the central nervous system consists of $\alpha 4$ and $\beta 2$ subunits (Flores et al. Mol. Pharmacol. 1992, 41, 31-37; Picciotto et al. 2001, Pharmacol. Ther. 92, 89-108). These $\alpha 4 \beta 2$ nicotinic acetylcholine receptors are possible targets for drugs to treat pain, nicotine addiction, and diseases like Alzheimer's and Parkinson's (Holladay et al., 1997, J. Med. Chem. 40, 4169-4194; Lloyd and Williams, 2000, J. Pharmacol. Exp. Ther, 292, 461-467)." See right column of first page of Zwart et al.

Another recent article disclosing the effects of neuronal nicotinic receptors also discloses similar findings of importance of these receptors based on the high interest in these receptors, i.e., the state of the art. See Exley et al., Br. J. Pharmacol. (2005), 146, 15-24, a copy of which is enclosed for Examiner's convenience. As stated therein:

"Neuronal nicotinic acetylcholine (nACh) receptors are currently the focus of considerable pharmaceutical interest because of their potential as therapeutic targets for a wide variety of brain diseases such as nicotine addiction, memory and learning disabilities, Parkinson's disease, Tourette's syndrome and Alzheimer's disease (Astles et al., 2002, Curr. Drug Targets – CNS Neurol. Disord., 1, 337-348)."

From the foregoing discussions it is very clear that the state of the art is quite matured with a great deal of work done in this area at least since 1992. Although it is admitted that medicinal chemistry is quite complex and not well understood, however, when there is clear showing of certain results, as presently shown in the instant invention, that should not be confused with art in general being unpredictable, as concluded by the Examiner.

Finally, the Examiner also alleges that there is not enough guidance and working examples. As we already discussed above, the specification is full of working examples, i.e., the specification discloses 72 well characterized compounds of this invention, as also admitted by the Examiner. In addition, as we also noted above, the specification provides specific *in vitro* binding test protocols and the data obtained for the compounds of the present invention. From this, one of ordinary skill in the art of medicinal chemistry readily appreciates that the compounds of the present invention are useful in the treatment of a variety of disorders associated with the dysfunction of nicotinic receptors. However, claims 3 and 5 have been amended to recite only a few of the specific disorders that can

be treated by the compounds of this invention. Therefore, it is respectfully submitted that claims 1-6, as amended, fully satisfy the requirements of 35 USC 112, first paragraph. Accordingly, withdrawal of rejection as to claims 1-6 is respectfully requested.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claim 1 stands rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In particular, the Examiner states that the claim refers to "base and salt forms of the compounds, a description of which is not found in the specification," with which Applicants respectfully disagree.

As already noted above, the specification provides ample description of base and salt forms at various places. For instance, at lines 11-13 it is clearly noted that the compounds of this invention can exist either in the free base form, i.e., as the free amine form of the formula (I) or can readily form salts with acids. In fact, as we noted above, compound 1 in Example 1 was first isolated as a free base (i.e., as a free amine) which was then converted to dihydrobromide by addition of hydrobromic acid to the free base, see detailed experimental procedure beginning at line 2, page 7, which concludes at line 17 in the isolation of the free base. Then the free base is converted to dihydrobromide following the procedures as described at line 17 to 20 of page 7 of the specification. Similarly, Examples 2 and 4 describe preparations of other hydrobromide salts of the invention. Whereas, Example 3 describes preparation of a free base. Additionally, various other salts and free bases of various compounds of the invention are summarized in Table, which begins at page 12 of the specification. Therefore, it is submitted that there is good description of the base and salt forms of the compounds in the specification. Nevertheless, claim 1 has been amended to recite more succinctly the "salt thereof" because the compound of formula (I) itself is a free base. Thus it is submitted that claim 1, as amended, fully satisfy the requirements of 35 USC 112, second paragraph. Accordingly, withdrawal of rejection as to claim 1 is respectfully requested.

Amendment to Specification

The Examiner has also objected to the use of trademark DOWEX® because it was written in lower case, i.e., Dowex®, although it was clearly marked with the registered trademark. Nevertheless, Applicants have amended the affected paragraph by way of this amendment. In addition, a generic terminology of "ion exchange resin" is also inserted.

Conclusions

In view of the above Remarks, it is respectfully submitted that claims 1 to 6, as amended, are now in condition for allowance and the early issuance of this case is respectfully requested. In the event the Examiner wishes to contact the undersigned regarding any matter, please call (collect if necessary) the telephone number listed below.

Applicants believe there are no fees due for this Rule 111 Amendment. However, if the Examiner deems that fees are due, please charge these fees to Deposit Account No. **18-1982** for sanofi-aventis U.S. LLC, Bridgewater, NJ. Please credit any overpayment to Deposit Account No. **18-1982**.

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Respectfully submitted,

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Enclosures: A copy of Zwart et al. (Eur. J. Pharmacology, April 5, 2006 (Epub ahead of print) (8 pages)
A copy of Exley et al., Br. J. Pharmacol. (2005), 146, 15-24 (10 pages)

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